

E2 USSN - 09/101,825

sequence, if any, is a non-natural or unusual amino acid other than a D-isomer of one of the genetically encoded amino acids.

78 (new). The polypeptide of claim 76 which is not more than 15 a.a. in length.

79 (new). The polypeptide of claim 77 which is not more than 15 a.a. in length.

Concluded

REMARKS

1. The only rejections still maintained against the present claims are "scope of enablement" rejections.

Before discussing these rejections, we wish to call the Examiner's attention to the relationship between this case and Larsen, USP 6,159,937 (copy enclosed). In that patent, claim 1 is drawn to

A substance which is

(I) a polypeptide amounting to 9 to 20 amino acids; said polypeptide comprising the following sequence:

X₁-X₂-X₃-Thr-X₄-Lys-X₅-Arg-X₆ (SEQ ID NO:22),
wherein

X₁ is Ala or Gly,

X₂ is Tyr or Phe,

X₃, X₄ and X₅ are independently selected from the group consisting of Met, Ile, Leu and Val; and

X₆ is selected from the group consisting of Asn, Asp, Gln and Glu,

and which has one or more of the following properties:

- (a) induces inhibition of spontaneous IL-8 production by human monocytes,
- (b) induces inhibition of IL-1 β induced IL-8 production by human peripheral blood mononuclear cells,
- (c) induces production of interleukin-1 receptor antagonistic protein (IRAP) by human monocytes,
- (d) induces chemotactic migration of CD8+ human T lymphocytes in vitro,
- (e) desensitizes human CD8+ T cells resulting in an unresponsiveness towards recombinant human IL-10 (rhIL-10),
- (f) suppresses the chemotactic response of CD4+ human T lymphocytes towards IL-8,
- (g) suppresses the chemotactic response of human

- monocytes towards MCAF/MCP-1,
- (h) induces the production of IL-4 by cultured normal human CD4+ T cells, or
- (i) reduces the TNF α production in human mixed leukocyte reaction, or,
- (II) a salt, ester or a conjugate of said polypeptide, but said conjugate is not IL-10 or a fragment of IL-10, which amounts to more than 20 amino acids of IL-10.

There is also a related application, 09/512,256, still pending. Its main claim is similar to that of the '937 patent except that it recites a length range of 6 to 100 amino acids.¹

Plainly, the present main claim (18) was modelled on the main claims of USP 6,159,937 and Serial No. 09/512,256. However, claim 18 as examined requires that at least one of conditions (I)-(V) be true, thereby avoiding double patenting relative to USP 6,159,937 or Serial No. 09/512,256:

A non-naturally occurring polypeptide, or a polypeptide in at least partially purified form, which is six to about 100 amino acids in length, and which comprises the following sequence

Thr-X₄-Lys-X₅-Arg-X₆ (SEQ ID NO:19),
wherein X₄ and X₅ are independently selected from the group consisting of Met, Ile, Leu and Val; and

X₆ is selected from the group consisting of Asn, Asp, Gln, and Glu,
wherein at least one of the following conditions (I)-(V) is true:

I) at least one of X₄, X₅, X₆, Thr, Lys, and Arg is independently substituted with a non-natural or unusual amino acid,

II) the polypeptide is cyclized,

III) the polypeptide is stabilized,

IV) the aminoterminal amino acid residue is acylated, or

V) the carboxyterminal amino acid residue is amidated,

if the polypeptide is not cyclized, said sequence corresponding essentially to the C-

¹ There is also, in the same patent family, USP 6,168,791, drawn to antibodies against these peptides.

terminal of said polypeptide

* * * *

[portion of claim omitted is identical to claim 1 of '937 patent.]

- h) inhibits class II MHC molecule expression on human monocytes stimulated by IFN- γ ,
- i) induces the production of IL-4 by cultured normal human CD4+ T cells,
- j) reduces TNF α production in human mixed leukocyte reaction, or
- k) downregulates TNF α and IL-8 production in a rabbit model of bile acid induced acute pancreatitis and reduces neutrophil infiltration in the lungs of the treated rabbits.²

According to the Examiner, the controversial aspects of claim 18 as examined are the upper limit of 100 on peptide length, and condition (I)'s reference to a "non-natural or unusual amino acid". (An "unusual" amino acid is one which occurs in nature, e.g., through post-translational modification, but is not one of the 20 genetically encoded amino acids.)

1.1. The first enablement rejection relates to the recited peptide, and, in particular, to both the length of the peptides and the choice of amino acids to be incorporated therein.

Claim 18, as examined, recited a maximum length of "about 100 amino acids". However, there is descriptive basis for shorter peptides at page 22, lines 21-25:

An interesting embodiment of the invention relates to a polypeptide of the invention where the number of amino acids amount in total from 6, 7, 8, 9 or 10 up to about 100 amino acids, e.g., 11, 12, 13, 14 or 15 amino acids, or even larger such as 20 amino acids or 30 amino acids.

² Activities "h" and "k" were not recited in the '937 patent.

In a telephonic interview on July 3, 2001, Examiner Hamud and SPE Gary Kunz agreed to accept a maximum length of 15 a.a. However, it seems to us that 20 a.a. should be allowed, given claim 1 of the '937 patent (but cp. claim 75).

Claim 18, as examined, also requires that one or more of the certain of the amino acids in question is a "non-natural or unusual amino acid"³. The Examiner complained that "all non-naturally occurring amino acids is an infinite genus". The Examiner did not express any concern vis-a-vis the utilization of any of the 20 genetically encoded L-amino acids, and explicit basis for them appears at page 17, lines 27-29.⁴ These are all α -amino acids.

Enclosed herewith is a report (Ex. A) on the preparation and testing of 33 synthetic peptide analogues of IT9302 (SEQ ID NO:1). These analogues included a cyclic peptide, a peptide with a C-terminal amidation, a peptide with N-terminal acylation, a dimer (with a $-\text{CH}(\text{NH}_2)-$ connecting group), five peptides with substitutions of genetically encoded AAs, and 24 peptides with non-natural or exotic amino acids. The latter were

Mea	N-(2-methoxyethyl) glycine
1Bua	N-isobutylglycine
β A	betaalanine
Cha	cyclohexylalanine
Pyu	pyridyl alanine
Met(O)	methionine-S-oxide
Nle	norleucine
Nva	norvaline

³ Clause (I) requires that at least one of positions 1-6 of SEQ ID NO:19 be so replaced. Claim 18 does not require that any of the remaining AAs, anywhere in the peptide, be "non-natural" or "unusual", but we agree that the recitation of "amino acids" would include these variations.

⁴ Technically speaking, glycine is not an L-amino acid, but the intent to include it was plain. —

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Orn ornithine

Dab 2,4-diaminobutyric acid

and the D-isomers of alanine (a), tyrosine (y), methionine (m), threonine (t), lysine (k), isoleucine (i), arginine (r) and asparagine (n).

Three tests were carried out. All analogues (but not IT9302) were tested in Test 2. All save six of the analogues elicited IRAP production higher than the control non-stimulated cells (14 ng/ml). However, of the six exceptions, four performed better than the control in Test 1 (17.2 ng/ml), and two were not tested in any other test run.

At least six analogues, all containing at least one non-natural or exotic AA, were held to be at least as potent as the original IT9302 peptide.

We also enclose a second report (Ex. B) giving mass spec analysis and peptide synthesis details for most if not all of the aforementioned analogues (identified in Ex. B as Mod13-Mod44). In the Table 1 sequences, boxes have been drawn around the hexapeptide core sequence corresponding to SEQ ID NO:19, and non-natural or unusual amino acids are underlined.

Finally, as Ex. C, we enclose a copy of a Gesser Declaration filed October 7, 1998 in Serial No. 08/765,094 (now USP 6,159,937), which describes a series of mutant peptides identified as "Mod1" through "Mod12".

In the interview, the Examiners conceded that there was basis for a Markush claim listing at least the exotic amino acids set forth at page 18, lines 1-29.

In view of Ex. A, it is essential that claim 18 cover peptides containing non-natural and unusual amino acids. Unfortunately, several of these amino acids⁵ are not listed on page 18, lines 1-29 and hence we cannot accept limitation to that

⁵ Specifically, Mea, 1 Bua, Cha, Pyu, and Met(O); "Dab" was listed as "Dbu".

list, absent some clear legal imperative to do so.

On the basis of the disclosure at page 17, lines 31-32, the Examiners conceded the propriety of reciting D-amino acids and β -amino acids corresponding to the aforementioned common and exotic amino acids. (cp. new claim 74, reciting alpha- and beta-amino acids). However, that does not solve the problem noted above.

Counsel also pointed to the reference to three catalogues that appears at page 18, line 30 to page 19, line 2:

Further and non-limiting examples of infrequently occurring, non-natural amino acids or building blocks are listed as follows: Novabiochem 1994/95 Catalog (Calbiochem-Novabiochem AG, Weidenmattweg 4, CH-4448 Läufelfingen/Switzerland), p. 65-125; Bachem Feinkemikalien AG 1995 Catalog (Bachem Feinkemikalien AG, Hauptstrasse 144, CH-4416 Bubendorf/Switzerland), pp. 753-831; Neosystem Laboratoire Catalogue 1997/98 (Neosystem Laboratoire, 7 rue de Boulogne, 67100 Strasbourg, France), pp. 131-176.

The Examiners expressed concern as to whether this citation constitutes an "incorporation by reference". While "mere reference" to another publication is not enough to "incorporate" material, see In re de Seversky, 177 USPQ 144 (CCPA 1973) (merely reciting that B is a "continuation-in-part" of A is insufficient to incorporate any part of A into B), what we have here is a clear expression of an intent to rely on the disclosure of the referenced catalogues to supply "non-limiting examples" of "non-natural amino acids". No case has held that this intent must be stated in particular words, i.e., "hereby incorporated by reference".

Indeed, such a holding would be inconsistent with case law interpreting the description requirement, where it has been held that it is not necessary that the exact words of the claim be used in the specification. See In re Lukach, 169 USPQ 795, 796 (CCPA 1971); In re Kaslow, 217 USPQ 1089, 1096 (Fed. Cir. 1983);

In re Smythe, 178 USPQ 279, 284-5 (CCPA 1973).

Hence, we are of the opinion that applicants may properly rely on the three catalogues. Moreover, we believe that these catalogues are relevant not only for the specific amino acids which they disclose, but also for what they may more broadly signify to one skilled in the art. That is, if they disclose a "Q derivative of one amino acid, they suggest a corresponding "Q" derivative of another, whether they sell it or not.

We are aware that a rather large number of amino acids are set forth in these catalogues, and hence would prefer to avoid reciting them all in a Markush group. One possibility is to take advantage of the "patterns" into which these amino acids fall.

For example, many of the amino acids in these catalogues are

- (a) one of the 20 genetically encoded amino acids;
- (b) D-isomers of (a) above;
- (c) amide (-NH₂ or -NHMe) derivative of (a) or (b) above;
- (d) an N-terminal or N-side-chain protected form of (a)-(c) above;⁶
- (e) a C-terminal or C-side-chain protected form of (a) or (b) above;⁷
- (f) amino acids with protected -OH or -SH side chains. (The value of protective groups in synthesis is recognized by page 20, lines 5-20 of the specification.)

The Novabiochem catalogue classifies its amino acids as derivatives of alanine, aminobutyric acid, aminohexanoic acid, amino isobutyric acid, amino suberic acid, arginine, asparagine,

⁶ For example, Ac-, Boc-, Bpoc-, FA-, B_z-, Fmoc, For-, Nps- and Z-.

⁷ For example, - α -naphthyl ester, - β -naphthyl ester, -ONP, -OSu, -OPfp, -2,4,5-trichlorophenyl ester, -OMe, -OtBu, -OtBzl, -OEt, -ONp.

aspartic acid, butylglycine, citrulline, cyclohexylalanine, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, norleucine, norvaline, ornithine, penicillamine, phenylalanine, phenylglycine, proline, pyroglutamic acid, sarcosine, serine, statine (and ACHPA and AHPPA), tetrahydro isoquinoline-3-carboxylic acid, thienylalanine, threonine, tryptophan, tyrosine, and valine. It also individually lists L-azetidine-carboxylic acid, L-carnitine, D-glucamine, H-Hci-OH (L-homocitrulline), 2R-(+)-propanolol HCl, 2S-(-)-propanolol HCl, L-thyroxine·Na, and 3,3',5-triiodo-L-thyronine·Na. Within these subclasses, besides the expected N- and C-terminal derivatives, we have various side chain derivatives.

The amino acids include not only alpha amino acids, but also beta (beta-alanine) and higher amino acids, e.g., gamma-aminobutyric acid.

The Neosystem catalogue first lists "natural amino acids and derivatives", and then "special amino acids". The latter include β -alanine, 2-amino benzoic acid (anthanilic acid), 4-aminobenzoic acid, 4-amino-1-benzoyl-pyrrolidine-2-carboxylic acid, 2-aminobutyric acid, 4-aminobutyric acid, 6-aminohexanoic acid, 8-amino octanoic acid, 3-amino-1-carboxymethyl-pyridine-2-one, 1-amino-1-cyclohexane carboxylic acid, 4(2-aminoethyl)-1-carboxymethyl-piperazine dihydrochloride, statine, AHMHpA, AHMHxA, AHPA, AHPBA, ANTHxA, AHIPA, AHPA, 2-aminoindane-2-carboxylic acid, 2-aminoisobutyric acid, (3-amino methyl)-benzoic acid, 2-aminotetraline-2-carboxylic acid, 5-aminopentanoic acid, 4-bromo-L-Phe, α -t-butyl Gly, 4-carboxymethyl-piperazine, 4-carboxymethyl piperidine, 2-carboxymorpholine, 4-chloro-L-Phe, β -cyclohexyl-L-alanine, N- α -Fmoc-N- α -Boc-diaminoacetic acid, N- α -Fmoc-N- γ -Alloc-L-diaminobutyric acid, N- α -Boc-N-B-Alloc-L-diaminopropionic acid, 3,4-dichloro-L-Phe, 4-fluoro-L-Phe, L-homoleucine, L-homoPhe, L-hydroxyproline, iminodiacetic acid, L-indoline-2-carboxylic acid, isonipecotic acid, 4-methyl-L-Phe, L-

1-naphthylalanine, L-2-naphthylalanine, 4-nitro-L-Phe, 3-nitro-L-tyr, norleucine, norvaline, ornithine, α -BOC-N- δ -Alloc-N-omithine, L-phenylglycine, $P(CH_2-PO_3Et_2)$ -L-Phe, 4-piperidyl-L-proline, 3-pyridylalanine, pyroglutamic acid, sarcosine, statine, L-tetrahydroisoquinidine-2-carboxylic acid, and so forth.

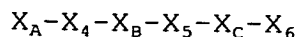
The BACHEM catalogue is similar in structure to the NOVOCHEM one. Besides listing derivatives of the 20 genetically encoded amino acids, it has sections for γ -carboxyglutamic acid, citrulline, cystine, hydroxyproline, norleucine, norvaline, ornithine, phenylglycine, pyroglutamic acid, sarcosine, statine, t-leucine, and a long list of individual "special amino acids", e.g., "Ac-p-aminohippuric acid".

It seems to us that if a limitation is to be imposed, the most logical one would be in terms of molecular weight. This would implicitly limit the number of atoms/complexity of the derivative. In the Neosystem catalogue, the highest MW amino acid is Fmoc-L-Lys(Trp)-OPfp, MW 745.6, on page 141 (catalogue no. FA01218). In the Bachem catalogue, it is, not counting certain dimers, Fmoc-His(Trt)-OPfp, MW 785.78, on page 782, catalogue no. B-1650. In the Novochem catalogue, it is L-Thyroxine, MW 776.9, catalogue number 04-11-0011. Therefore, if the nature of the amino acid must be explicitly limited, we would suggest consideration of the limitation, "where each of said remaining amino acids has a molecular weight which is not greater than that of Fmoc-His(Trt)-OPfp" (see new claim 73).

1.3. There is a further technical problem, pointed out at the interview, with the construction of claim 18 as examined. Claim 18 requires that the peptide "comprise" SEQ ID NO:19. However, clause (I) allows one or more of the six positions of SEQ ID NO:19 to be replaced with a "non-natural or unusual amino acid". If such a replacement were made, the peptide would no longer "comprise" SEQ ID NO:19.

We have decided to handle this drafting problem in the following manner:

(1) Claim 18 has been amended to recite the sequence



(2) X_A is defined as L-Thr or D-Thr,

(3) X_4 and X_5 have been broadened to include norvaline (Nva) (see Mod 26), norleucine (Nle) (see Mod 25), methionine-S-oxide (Met(O)) (see Mod31), cyclohexyl alanine (see Mod29), N-methylvaline (MeVal), N-methylisoleucine (MeIle), and allo-Isoleucine (aIle), and the D-forms of all of the recited L-amino acids;

(4) X_B is defined as L-Lys, L-Orn (see Mod27), L-Dab (see Mod 28), and their D-forms;

(5) X_C is defined as L-Arg and D-Arg; and

(6) X_6 has been broadened to include the D-forms of the respective amino acids.

X_A replaces the original recitation of "Thr", and the examiner has conceded basis for use of a D-isomer. Similarly, X_C replaces the original recitation of "Arg", and X_6 of the four acidic L-amino acids. X_4 and X_5 , originally directed to Met, Ile, Leu and Val, have been broadened to include the similar amino acids listed at page 18, lines 1-29, or appearing in the X_4 or X_5 position in Exs. A and B, and also the various D-forms. Finally, X_B , originally "Lys", has been broadened to include Orn, Dab, and the various D-isomers, again in view of Exhibits A and B.

Note that while the formal definitions of X_A , X_B , X_C , X_4 , X_5 , and X_6 have been broadened, the allowed substitutions at each of these positions has actually been narrowed, as clause (I) allowed any of these positions to feature any "non-natural or unusual amino acid". Each of the recited amino acids is available from at least one of the three cited catalogues.

Thus, we have limited the choice of "core sequence" amino acids to those specified by our definitions of X_A , X_B , X_C , X_4 , X_5 and X_6 . However, for the flanking amino acids, we think we are entitled to a broader range, consistent with the catalogue

disclosures.

With regard to the assertion that the term "non-naturally occurring amino acid" [sic] encompasses infinite possibilities, we must respectfully point out that the same statement could be made concerning many of the chemical classes recited in patent claims. For example, there are an infinite number of "esters and salts", but it is not unusual for a claim to a drug to end "or an ester or salt thereof". It is common for organic compound claims to recite "alkyl" groups, and, unless a size limitation is imposed, there are an infinite number of those, too.

Nonetheless, we would consider flanking AA limitations which would not exclude β Ala (Mod 15), Cha (Mod 16), iBua (Mods 17 and 18), Mea (Mods 1) and 20), Pya (Mod 21), Met(O) (Mod 22), Nle (Mod 23), Nva (Mod 24) and related D-amino acids (Mods 35, 36, 37, 41).

New claim 76 takes a different tack. Instead of limiting the choice of non-natural or unusual amino acids at positions X_A , X_B , X_C , X_4 , X_5 and X_6 , it limits the number of such amino acids which can be introduced at those positions, with the exception of D-isomers of the recited L-amino acids. Thus, if X_B is L-Orn, then X_4 could be D-Met, D-Ile, D-Leu, or D-Val, but no other D-isomer and no other non-natural or unusual amino acid. See also claims 77-79.

2. The second enablement issue relates to the scope of the method claims. The examiner concedes enablement only for treatment (not prevention) of pancreatitis (not other diseases).

2.1. We believe that we have evidence that our peptides are useful in the prevention of mortality due to pancreatitis. As described in the enclosed article, Osman, et al., Surgery:124:584 (1998) rabbits were pretreated with either intravenous saline or with IT9302. Thirty minutes later, acute necrotizing pancreatitis was induced by retrograde injection of 5% chenodeoxycholic acid in the pancreatic duct, followed by duct ligation. The effects of the pretreatment were similar to those

described in the specification vis-a-vis treatment, see page 48, lines 20-25.

We do not assert that the "prevention" is absolute, only that it occurs to a clinically beneficial degree.

2.2. With regard to the "litany of diseases" in claims 42-44, the Examiner fails to make out a prima facie case of nonenablement for treatment. All of the diseases in question are believed to be affected by IL-10 activity (see Table 2).

Hence, there is reason to believe that they can be affected by the claimed analogues of IT9302, a peptide with IL-10-like activity.

The Examiner gives too little weight to (1) IL-10's known role in mediating the recited diseases, (2) use of the anti-pancreatitis dosage level as a starting dose for other diseases, (3) Ex. 11, showing prevention of leukopenia in pigs, (4) Ex. 16, showing use of IT9302 against HPV, and Ex. 17, against chronic joint pains, and (5) the teachings of dosages at page 25, lines 1-12, and of routes of administration at page 23, line 24 to page 24, line 2 and page 24, lines 22 to 34.

The Examiner gives too much weight to the number of diseases implicated. There are no lack of antibiotics, hormones, vitamins, etc., that affect quite a few diseases. One need not find an "elixir for the Gods" to find a peptide that can treat a variety of IL-10-regulated diseases.

2.3. Claims 42-46 have been cancelled, so the main method of use claims are 49 and 50. Claims 49 and 50 were not included in the "disease" rejection (OAp. 7). Somewhat inconsistently, dependent (on 49) claims 51-53, 61, 63 and, 69-72 were so rejected.⁸ But dependent claims 57 and 59 were not.

3. Claims 48, 54-56, 58, 60, 62 and 64 have been cancelled

⁸ Hence, if the Examiner, in the next action, chooses to reject those claims on this ground, the action cannot be made "final", as the rejection could have been made in the January 30, 2001 office action.

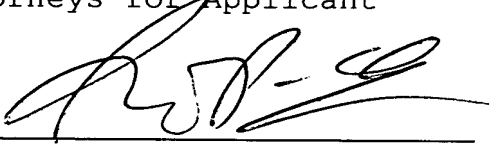
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without prejudice or disclaimer so that their subject matter may be pursued in Serial No. 09/512,256.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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Attorneys for Applicant

By: 
Iver P. Cooper
Reg. No. 28,005

Enclosures

-Osman (1998)
-Exhibit A
-Exhibit B
-Exhibit C
-Larsen, USP 6,159,937
624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone: (202) 628-5197
Facsimile: (202) 737-3528
IPC:lms
F:\,P\Plou\Gronhoj\Larsen2\ptoamend2.wpd

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Please cancel claims 42-46, 48, 54, 55, 56, 58, 60, 62, and 64.

Claims 18 and 41 have been amended as follows:

18 (twice amended). A non-naturally occurring polypeptide, or a polypeptide in at least partially purified form, which is six to 20 [about 100] amino acids in length, and which comprises the following sequence

[Thr-X₄-Lys-X₅-Arg-X₆ (SEQ ID NO:19)],

X_A-X₄-X_B-X₅-X_C-X₆

wherein X₄ and X₅ are independently selected from the group consisting of Met, Ile, Leu, [and] Val, norvaline, norleucine, methionine-S-oxide, N-methylvaline, N-methyl isoleucine, allo-leucine, and their D-isomers; [and]

X₆ is selected from the group consisting of Asn, Asp, Gln, [and] Glu, and their D-isomers,

X_A is L-Thr or D-Thr,

X_B is L-Lys, L-Orn, L-Dab, or one of their D-isomers, and

X_C is L-Arg or D-Arg,

wherein at least one of the following conditions (I)-(V) is true:

I) at least one of [X₄, X₅, X₆, Thr, Lys, and Arg] X_A, X_B, X_C, X₄, X₅ or X₆ is [independently substituted with] a non-natural or unusual amino acid,

II) the polypeptide is cyclized,

III) the polypeptide is stabilized,

IV) the aminoterminal amino acid residue is acylated, or

V) the carboxyterminal amino acid residue is amidated, where, if the polypeptide is not cyclized, said sequence [SEQ ID NO:19 corresponding] corresponds essentially to the C-terminal of said polypeptide,

said polypeptide having at least one of the following properties:

a) induces inhibition of spontaneous IL-8 production by

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human monocytes,

b) induces inhibition of IL-1 β induced IL-8 production by human peripheral blood mononuclear cells (PBMC),

c) induces production of interleukin-1 receptor antagonistic protein (IRAP) by human monocytes,

d) induces chemotactic migration of CD8+ human T lymphocytes in vitro,

e) desensitizes human CD8+ T cells resulting in an unresponsiveness towards rhIL-10,

f) suppresses the chemotactic response of CD4+ T human lymphocytes towards IL-8,

g) suppresses the chemotactic response of human monocytes towards MCAF/MCP-1,

h) inhibits class II MHC molecule expression on human monocytes stimulated by IFN- γ ,

i) induces the production of IL-4 by cultured normal human CD4+ T cells,

j) reduces TNF α production in human mixed leukocyte reaction, or

k) downregulates TNF α and IL-8 production in a rabbit model of bile acid induced acute pancreatitis and reduces neutrophil infiltration in the lungs of the treated rabbits.

41 (amended). A pharmaceutical composition comprising a polypeptide according to claim 18, or a salt, ester or solvate of said polypeptide[, or a peptidomimetic modelled on the basis of said polypeptide].

Claims 73-79 have been added.